REMARKS

Claims 33 and 44 have been amended. Thus, claims 33-64 remain pending in the application, with claims 33-59 currently under examination. Reconsideration and withdrawal of the present objection and rejections in view of the comments presented herein are respectfully requested.

Sequence Rules and Objection to the specification

The Examiner objected to the specification because it recited a sequence that was not identified by SEQ ID NO: (page 71, line 30). The Examiner also noted that the present application did not contain a sequence listing. The specification has been amended to identify the sequence at page 71, line 30 as SEQ ID NO: 39. In addition, enclosed herewith is an electronic copy of the sequence listing which includes all of the sequences in the application as originally filed, including newly designated SEQ ID NO: 39.

All of the sequences in the enclosed Sequence Listing were included in the application as originally filed. Pursuant to 37 C.F.R. § 1.821 (g), no new matter is being added herewith. Since the sequence listing is being filed electronically, there is no paper copy thereof. Accordingly, a statement that the electronic and paper copies are identical cannot be made. However, as required under 37 C.F.R. § 1.821(f), I hereby verify that the sequence information in the enclosed sequence listing is identical to the sequences in the application as filed on July 22, 2005.

Rejections under 35 U.S.C. § 103(a)

Claims 33-44, 46 and 55-59 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Eads et al. (Nucleic Acids Res. 28:e32 i-viii, 2000), in view of Christensen et al. (Nucleic Acids Res. 30:4918-4925, 2002).

Claims 45 and 47-54 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Eads et al. (Nucleic Acids Res. 28:e32 i-viii, 2000), in view of Christensen et al. (Nucleic Acids Res. 30:4918-4925, 2002), and further in view of Shah et al. (US 5,629,156).

With regard to claims 33-44, 46, and 55-59, the Examiner alleges that Eads teaches all of the steps of the claimed method, with the exception of an intercalating nucleic acid (INA) to detect the target nucleic acid, and that it would have been obvious to modify the method of Eads

with a step of using an INA to achieve the expected advantage of developing a sensitive method to discriminate between DNA/DNA and DNA/RNA hybrids.

With regard to claims 45 and 47-54, the Examiner contends that, although neither Eads et al. nor Christensen et al. teach the use of a capture ligand and solid support to immobilize target nucleic acid, it would have been obvious to modify the method of Eads et al. and Christensen et al. with the step of adding a capture ligand to achieve the expected benefit of developing an enhanced and improved method for detecting a nucleic acid. However, as explained in detail below, neither of these combinations of references would render the presently claimed invention obvious.

Eads et al. disclose detection of methylation in clinical samples using well-known fluorescent based real time PCR (TaqMan). As noted in paragraph 6 of the enclosed Declaration of Douglas Spencer Millar under 37 C.F.R. § 1.132, this method uses conventional oligonucleotides, PCR primers and a specific oligonucleotide that has been labeled with a reporter and quencher group to detect the presence of specific target molecules, and relies on amplification of the target molecule by PCR to produce enough molecules to be detected by real time TaqMan probes. Neither Eads et al nor Christensen et al. teach or suggest the use of INA molecules as either primers or probes in any type of amplification reaction, nor had such amplification of conventional or bisulfite-treated DNA using INAs been performed prior to the present invention (Declaration, paragraph 7). Thus, one skilled in the art would not have had an expectation that INAs would work in such procedures.

According to M.P.E.P. 2143.01, "if [the] proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)." As noted in the enclosed Rule 132 Declaration of Douglas Spencer Millar (paragraph 8), the INA primers of Christensen et al. would not be expected to work if used in the amplification reaction of Eads et al since the amplification enzyme (Taq polymerase) would not be expected to be able to extend past the INA due to the addition of the intercalator pseudonucleotide (IPN) group which would hinder primer extension.

In addition, if the IPN or multiple IPNs are placed near or at the 3' end of the INA, the IPN blocks extension by Taq resulting in no amplification of the desired target sequence (Declaration, paragraph 9). Furthermore, the INAs would not be expected to work properly in a

TaqMan protocol (as disclosed by Eads et al.) as their inherent nuclease resistant properties, already disclosed by Christensen et al, would be expected to prevent probe hydrolysis thus stopping the reaction (Declaration, paragraph 9).

Thus, in view of the hindering effect of the INA on the Taq polymerase, and their inherent nuclease resistant properties, one of ordinary skill in the art would certainly not be motivated to use an INA as disclosed by Christensen et al. in the method of Eads et al. because the method of Eads et al. would no longer work for its intended purpose. In addition, one skilled in the art would not have a reasonable expectation of success if INAs were used in the methods of Christensen. Accordingly, the claims cannot be obvious in view of this combination of references, or this combination further in view of Shah et al.

In addition, with respect to Claim 38, as discussed in paragraph 10 of the Declaration, when using bisulfite treated DNA the Tm of the primers are significantly lower that the equivalent Tm of a primers using wild type, untreated DNA. This can result in the amplification of artefacts due to the low temperatures required in the annealing step of the amplification or low stringency hybridization steps which can cause false positive amplification/hybridization signals, which is a significant problem when using bisulfite treated samples and can result in having to perform two round nested PCR reactions to improve specificity, or to use internal probes as was done by Eads et al. This property of bisulfite treated DNA can also severely reduce the specificity in hybridization bases approaches using conventional oligonucleotides. However, INAs unexpectedly increase the Tm at which the amplification or hybridization reactions can be done using bisulfite treated DNA as a template to improve specificity. The beneficial effects of INA on Tm of bisulfite treated DNA are also discussed in the present specification at pages 48-49, and noted in the Declaration at paragraph 10.

The teachings of Christensen et al. and Shah et al. are based on conventional 4 base genomes containing roughly equal amounts of the bases G, A, T and C. However, as recited in claim 38, bisulfite treatment modifies cytosine into uracil. It is not possible to translate the teachings disclosed in these references to a situation in which one of the four bases, namely C, has been substantially removed, resulting in a genome which is comprised essentially of G, A and T. Thus, it would not be obvious that an INA used in this situation would dramatically improve the thermal stability since CG base pairing has been significantly reduced, and it is this base pair that is the most stable and contributes most to thermal stability.

The beneficial effects described above could not have been predicted based on any of the cited references, alone or in combination, and would effectively rebut any *prima facie* allegation of obviousness.

With respect to claim 47, none of Eads et al, Christensen et al or Shah et al have successfully coupled an INA molecule to any form of solid support and demonstrated that it is still suitable as a substrate for hybridizations with complementary DNA, nor have they used INAs in a non-amplified sample to detect the presence of specific target sequences. Applicants submit that, prior to the present invention, one of skill in the art would not have a reasonable expectation that such procedures would be effective.

In view of the comments presented above, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a).

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

Applicants submit that all claims are in condition for allowance. However, if minor matters remain, the Examiner is invited to contact the undersigned at the telephone number provided below. No fees are believed to be due. However, please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 3/12/08

By: _____

Neil S. Bartfeld, Ph.D.
Registration No. 39,901
Agent of Record
Customer No. 20,995
(619) 235-8550

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